UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,922	03/12/2004	Hans Ernst Jan Hofland	020681-001610	6834

20350 7590 02/21/2008

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
02/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,922	HOFLAND ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-37* is/are pending in the application.

4a) Of the above claim(s) *7-10 and 12-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 1-17-08 is acknowledged.

Claims included in the prosecution are 1-3, 5-6 and 11.

Claim Rejections - 35 USC § 112

1. Claims 1-3, 5-6 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant introduces the expression, "said infection is caused by an infectious agent having a ***lipid bilayer".*** There is no support for this expression in the specification as originally filed and therefore deemed to be new matter. Instant specification does not teach what agents have a lipid bilayer.

2. Claims 1-3, 5-6 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro inhibition of HSV and HIV by octylglycerol containing liposomes, does not reasonably provide enablement for generic 'single chain lipid active agent' and prevention of infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d, 1400 (Fed.Cir.1988). Among these factors are: (1) the nature of the invention; 2) the state of the prior art; 3) the relative skill of those in the art; 4) the predictability or unpredictability of the art; 5) the breadth of the claims; 6) the amount of direction or guidance presented; 7) the presence or absence of working examples; and 8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

1) The nature of the invention: the invention concerns with a method of prevention of an infection using a liposomal formulation containing a single chain lipid.

2) The state of the prior art: the state of the prior art is very high in terms of formulating the liposomal compositions containing specific drugs for the treatment of various diseases but not preventing disease with a generic term, infection which can be due to any microorganism.

3) The relative skill of those in the art: the skill of one of ordinary skill in the art is very high (Ph.D level technology).

4) The predictability or unpredictability in the art: while there is general predictability in formulating the liposomal or proliposomal formulations, there is unpredictability in the art of preventing disease states such as AIDS, HSV infections and other viral diseases. Infections can be caused by any organism including, viruses, bacteria, micobacteria, fungi and parasites. Just because one specific compound (octyl glycerol) inhibits a

specific virus in vitro, one cannot extrapolate the results to prevention of the infection by that specific virus in vivo by any other single chain lipid, let alone prevent any infection caused by any other infectious agent. Recent well-known example of drug resistant strain of tuberculosis can be cited as interest. Furthermore, in vitro studies may or may not be enough to predict a compound's effect in vivo and the examiner cites the reference of Zips (In Vivo, 19, pp. 1-8, 2005) in this context (see page 1 (Translational research chain in evaluation of anticancer agents on col. 2, page 1 and page 3, col. 2, last but one para).

5). The breadth of the claims: instant claim is very broad in terms of the active agent and the disease to be prevented. Said claim 1 does not recite any specific active agent and the specific disease to be prevented. The term, 'single chain lipid active agent' includes multitudes of compounds including fatty acids, fatty acid esters and any aliphatic or aromatic compound containing a single fatty acid chain. Furthermore, as pointed out above, infections can be causes by any microorganism and even in the elected species, 'viral infections', there are RNA and DNA viruses each acting by different mechanisms at any time and it is impossible to determine when the individual will be exposed to any specific microbial agent and prevent such an exposure or prevent the subsequent infection.

6) The amount of direction of guidance provided: instant specification provides no guidance at all in terms of preventing diseases states.

7) The presence or absence of working examples: as pointed out above, infection can be caused by any microorganism and instant specification provides no working

examples as to how the diseases can be prevented using the claimed formulation. What is shown in the examples is the use of one specific compound, 'octylglycerol' on specific viruses HSV and HIV in vitro.

8) The quantity of experimentation necessary: since the claim 1 does not recite any specific active agent and prevention of any specific disease state, it is difficult for one of ordinary skill in the art to choose the proper active agent and prevent a disease without undue experimentation.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that the claims have been amended to recite "wherein the lipid moiety of said single chain lipid active agent is required for prevention of said infection and wherein said infection is caused by an infectious agent having a bilayer and therefore the claims are no longer subject to the above rejection. This argument is confusing since the rejection is based on the claims reciting ***'prevention'*** (not treatment of the infection) and it is unclear how the amendment would overcome the rejection. Applicant on page 9 of the response state that as amended, the independent claim 1 recites methods for treating infections caused by agents having a lipid bilayer, the common feature exploited in the current invention. This argument is once again confusing since the claims are not drawn to a method of ***treating an infection***, but rather to prevention of the infection. The same response is deemed applicable to applicant's arguments on pages 10-11.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-3, 5-6 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear as to what applicant intends to convey by 'infectious agent having a lipid bilayer' in claim 1. What agents have a lipid bilayer? Instant specification does not adequately teach as to what agents have a lipid bilayer.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-3, 5-6 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Hostetler (US 2001/0033862).

Hostetler teaches liposomal formulations containing single chain lipids for the inactivation of HIV virus (abstract, 0034-0042; 0050-0051; 0155-0156; claims).

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that Hostetler does not teach lipid active agents for preventing infections resulting from infectious agents having lipid bilayers. This argument is rather confusing since instant claim 6 recites the same virus as the infectious agent as taught in Hostetler. Applicant further argues that the lipid derivatives in Hostetler, as evidenced by the Abstract, are effective in improving the efficacy of antiviral nucleoside analogues by prolonging the antiviral activity after the administration of the drug has ended and as

such the Hostetler art teaches antiviral compounds that work by inhibiting viral polymerases with nucleoside analog active agents and not by targeting the lipid bilayer with single chain lipid active agents, as in the instant invention. This argument is not persuasive since Hostetler teaches the inactivation of the virus, which means the infection is prevented and the mechanism by which the composition acts is not pertinent. In addition, instant claims do not exclude the drug acting by polymerase inhibition.

7. Claims 1-2, 4-5 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Spevak (J. Am. Chem. Soc., vol. 115, pp. 1146-1147 (1993).

Spevak teaches the inhibitory effect of influenza virus by liposomes containing a single chain lipid (pages 1146-1147).

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues the following. "Spevak et al., while disclosing lipid derivatives of O-sialosides, do not teach single chain lipid active agents, wherein the lipid moiety of said single chain lipid active agent is required for preventing infections resulting from infectious agents having lipid bilayers. The lipid derivatives taught in Spevak et al. act though O-sialoside binding to hemagglutinin, as evidenced by lines 1-5 of column one on page 1146: *The surface lectin of the influenza virus, hemagglutinin, binds to terminal o~-glycosides of N-acetylneuraminic acid ~euAc) on cell-surface glycoproteins and glycolipids. Viral binding to cells expressing terminal NeuAe residues can be inhibited by a-O-glycosides of NeuAe (O-* sialosides*).* As such, Spevak et al. teach the functional use of O-sialosides and merely use the lipid derivation to aid in delivery. This is in stark

contrast to the instant application, which teaches the use of single chain lipids as the active agent to prevent infections. As such, Spevak et al teach the functional use of)-sialosides and merely use the lipid derivatation to aid in delivery".

These arguments are not persuasive since instant claims merely recite 'single chain lipid active agent' and therefore, do not exclude single chain derivatives of 'sialosides' and since the reference teaches the use of single chain lipids for the influenza viruses, the reference is applicable.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-3, 5-6 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eibl (US 2002/0173489) in combination with Ho (US 2004/0208921, Hostetler (US 2001/0033862), Firshein (6,121,245) individually or in combination.

Eibl discloses formulations containing single chain lipids, which include alkylglycerols for viral infections such as HIV (0028, 0049-0057, 0064-0066, 0089,

claims, claims 21, 26, 49, 51, 52, 54 and 57). What is lacking in Eibl is the teaching of the use of liposomes as carriers for the alkylglycerols.

Ho while disclosing liposomal formulations containing drugs for targeted delivery to lymphoid tissues teaches the advantages of liposomes or lipid complexes. According to Ho, as drug delivery systems, liposomes are especially promising because they can modulate the pharmacokinetics of liposome-associated drugs, which is not possible with non-lipid associated, or free drugs. Any number or combinations of lipid-anti HIV drug or lipid-anti-HIV biological complexes can be subcutaneously injected into HIV infected mammalian subject so that high concentrations of stable lipid-drug complexes can be preferentially delivered to the lymphoid tissue via lymphatic vessels, instead of delivering intravenously and HIV reservoirs within the infected lymphoid cells can be targeted effectively (abstract, 0004, 0009, 0013-0015, 0028, 0031, 0033, 0035, examples and claims). One of the lipids, which could be used, in addition in the liposomes is monoglycerides (alkylglycerols) (0034).

Hostetler while disclosing a method of treating viral infections teaches that in the form of liposomes, the antiviral agents are preferentially taken up by macrophages and monocytes, cells which have been found to harbor the target HIV virus (abstract, 0014, 0050 and 0051).

Firshein teaches while disclosing a method of treating cancer using alkylglycerols teaches that these compounds that these compounds can be incorporated into liposomes and that ordinary glycerol ethers, after incorporation into phospholipids, can activated the body's immune defense system (col. 4, lines 55-61; col. 10, lines 4-20).

It would have been obvious to one of ordinary skill in the art to use liposomes as carriers for alkylglycerols taught by Eibl because of the advantages of liposomes taught by Ho, Hostetler and Firshein.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that none of the cited references teach or suggest using a single chain lipid active agent, wherein the lipid moiety of said single chain lipid active agent is required for prevention of said infection. In particular, applicant argues that Eibl reference teaches "compounds and compositions that are particularly useful in the treatment of conditions involving viruses with a lipid membrane (0089). According to applicant, as such these compounds would not be effective in preventing infections as they rely on modifying a host's immune response, would be activated only after infection and conversely according to applicant that the compositions taught in instant application do not rely on the host organism as evidenced by examples 1 and 2 which show activity in vitro. These arguments are not persuasive since the prior art teaches the same alkylglycerols as in instant invention and as recognized by applicants themselves Eibl teaches the effectiveness of these against viruses with a lipid membrane and instant claims recite lipid membranes. Furthermore, instant examples show the in vitro effectiveness of the compounds against the viruses and not preventing the infection itself. Third, as pointed out above, the mechanism by which the composition acts has no significance since the compositions (alkylglycerol) and the infectious agents are the same in both prior art and in instant invention. Finally, since viruses such as HIV remain dormant and the antiviral agents actually prevent the proliferation of the virus and not

actually prevent the virus from entering the host (actual prevention), one can construe that the prior art actually prevents the virus infection just as in instant case. Therefore, applicant's arguments that the secondary references do not teach the prevention as argued on page 15 of the response are not persuasive.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ S Kishore

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1612

GSK